BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Intracranial Drug Administration in Alzheimer's Disease

Robert E. Harbaugh, M.D.[1]

Introduction

During the last decade there has been an explosion of information regarding the neurochemical activity of the central nervous system (CNS). The identification of numerous neurotransmitter, neuromodulator, and neurohormone candidates, and the elucidation of their roles in normal and pathological brain function, have vastly expanded the possibilities for pharmacologic manipulation in the treatment of neurologic disease.

Clinical application of this neurochemical information has, however, been plagued by difficulties with drug delivery to the CNS. Long-standing problems in clinical neuropharmacology include adverse systemic effects of neuroactive drugs, peripheral metabolism or inactivation of drugs, difficulties with blood-brain barrier penetration, erratic drug absorption and binding by serum proteins, adverse effects at one level of the neuraxis to achieve therapeutic effects at another (e.g., sedation with narcotic analgesics), and problems with patient compliance. One can think of few neuroactive drugs where at least one of these problems is not clinically significant. In addition, a number of potentially therapeutic compounds may never reach clinical trials because of these problems.

With implantable drug infusion devices and stereotactic neurosurgical techniques, the technology is available today to circumvent all of the above difficulties. Direct infusion of drugs into the cerebrospinal fluid (CSF) bypasses the problems of systemic side effects, peripheral drug inactivation, poor drug absorption, serum protein binding, and blood-brain barrier penetration. Continuous or programmable drug infusion devices ensure patient compliance. Regional drug infusions can obviate adverse effects at other levels of the neuraxis and it may, in time, be possible to infuse minute quantities of drugs directly into circumscribed areas of the brain parenchyma, thereby achieving neuroanatomically precise pharmacologic manipulations of brain function.

The rationale behind drug delivery to the CNS by central infusion and selection criteria for drugs for infusion will be briefly discussed. Experience here with central drug infusion for patients with Alzheimer's disease (Harbaugh et al., 1984) will be used to illustrate the application of this technology in a clinical setting. Potential complications of this treatment approach will also be discussed.

Rationale Of Central Drug Infusion

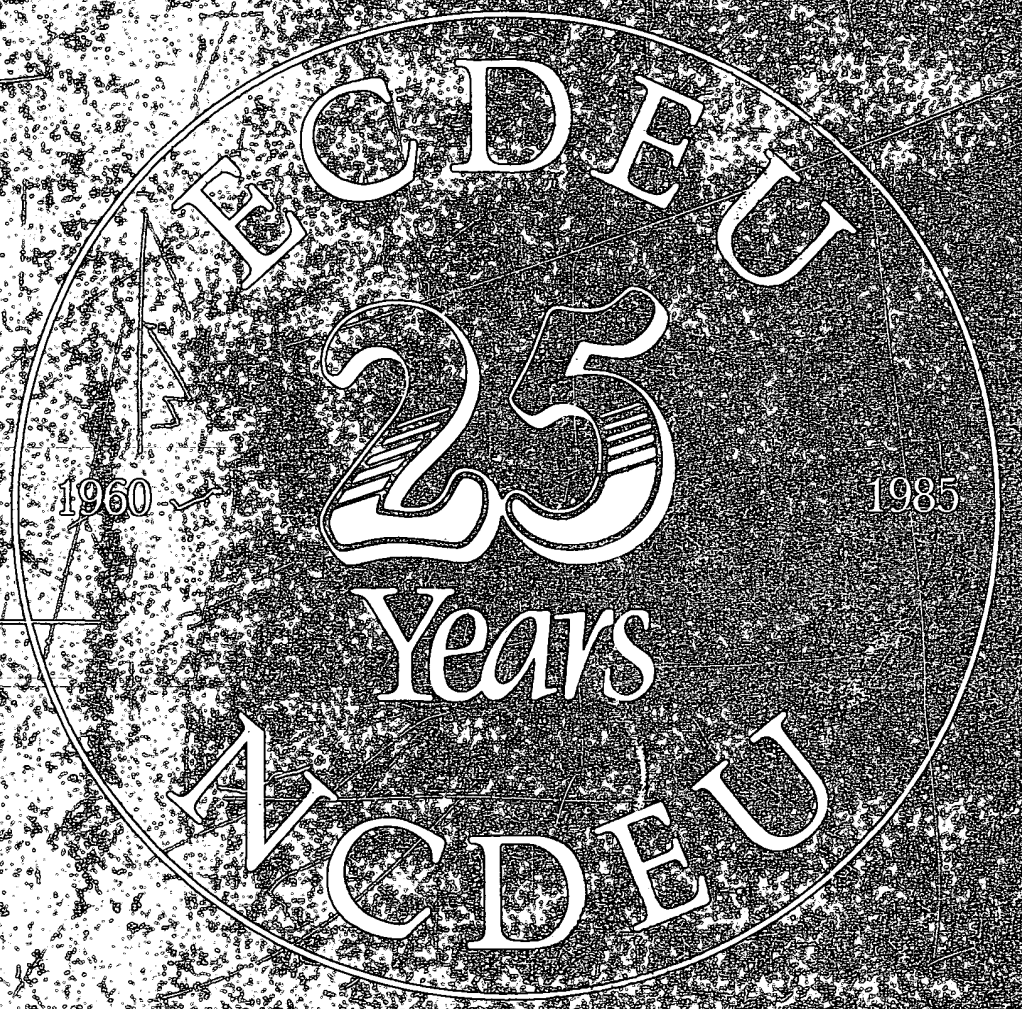
By and large, intrathecal drug administration has not proven to be effective (Aird, 1984). Therefore, the first question to be addressed regarding central drug infusion is whether these drugs achieve adequate brain penetration. The answer to this question depends not only on the drug involved but also on the method of central drug administration.

Most clinical trials of central drug administration have employed single or intermittent bolus injections into the subarachnoid space or ventricular system. Of all the ways to deliver drugs to the CNS, this is probably the worst. Single bolus injections result in very high CSF drug concentrations and relatively limited parenchymal penetration (Blasberg et al., 1977; Lee et al., 1960). In addition, a single large bolus of drug is likely to be more toxic and less effective than more frequent, smaller doses (Bleyer et al., 1978). However, even with bolus administration, drugs will penetrate the parenchyma and, as CSF is cleared by bulk flow, diffuse back into the subarachnoid space (Blasberg et al., 1977). In situations where high drug concentrations in the CSF or immediately adjacent parenchyma

[1]Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, Hanover, NH 03756.

PSYCHOPHARMACOLOGY BULLETIN

NATIONAL INSTITUTE OF MENTAL HEALTH



1986

Vol. 22, No. 1

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration

are desired (carcinomatous meningitis, spinal anesthesia/analgesia, chemical rhizotomy), bolus injections are effective. However, if deeper diffusion into parenchyma is necessary, longer term infusion is preferable.

Intravascular administration of drugs which cross the blood-brain barrier shows a rapid onset of action due to the short circulation time and extensive vascular-CNS interface (Aird, 1984). However, drugs administered into the CSF require much longer for adequate diffusion into the parenchyma (Lee et al., 1960). As the duration of central drug administration increases, the depth of parenchymal penetration, even of large protein molecules, also increases (Brightman et al., 1969). Therefore, to adequately evaluate the effectiveness of central drug administration, infusions must be carried out over a prolonged time.

In addition to the duration of central drug infusion, the rate of infusion may be important. Rates of infusion rapid enough to elevate CSF pressure will result in increased CSF absorption and therefore increase drug elimination by bulk flow (Katzman et al., 1970).

The site of infusion within the central compartment may also be of significance. Drug penetration into the parenchyma appears to occur more readily through the ependymal than the pial surface (Rall, 1968), and drugs administered into the subarachnoid space may not enter the ventricular system (Yen et al., 1978). Therefore, intraventricular drug infusion is a more reasonable approach for achieving diffuse brain penetration than is lumbar intrathecal administration. Conversely, if one wishes to confine drug effects to the spinal cord with minimal effects at higher levels of the neuraxis, then intraspinal infusion may be beneficial (Coombs et al., 1983; Harbaugh et al., 1982). Thus, some relatively restricted neuropharmacologic effects can be achieved. Theoretically, with stereotactic cannula placement and very low flow-rate infusion devices, delivery of minute quantities of drugs to very circumscribed regions of brain parenchyma is possible.

When evaluating the effectiveness of central drug administration, the choice of drug is at least as important as the method of delivery. The ability of a drug to cross the blood-brain barrier is more likely to be detrimental than beneficial if the drug is given as a continuous central infusion. Drugs which readily cross brain capillaries can be rapidly cleared from the CNS when infused into the CSF (Blasberg et al., 1975). The use of such drugs may be valuable if high local concentrations in tissue adjacent to the subarachnoid space or ependyma are desired. However, if deeper parenchymal penetration is the goal, then lipid insoluble, polar molecules are better candidates for infusion (Blasberg et al., 1975).

When considering drugs for long-term central infusion, chemical and biological stability become important criteria. For continuous infusion via an implantable pump, the infused drug must be stable at body temperature for at least as long as the cycle time of the infusion pump. In addition, if widespread diffusion of active drug into parenchyma is desired, then the drug infused cannot be rapidly metabolized within the CNS or CSF. This last consideration may not apply to local intraparenchymal infusion where a steep concentration gradient of active drug could be beneficial.

Clinical Experience

Our clinical experience at Dartmouth (Coombs et al., 1983; Harbaugh et al., 1982, 1984) with implantable infusion devices for central drug administration may serve to illustrate some of the points raised above. The clinical studies referred to were approved by our institution's committee for the protection of human subjects and informed consent was obtained before instituting any experimental treatment trials.

The evidence for the cholinergic hypothesis of Alzheimer's disease has been extensively reviewed (Coyle et al., 1983) and need not be repeated here. If this cholinergic hypothesis is correct, then augmentation of brain cholinergic activity may ameliorate some of the symptoms in these patients. Previous attempts at increasing brain cholinergic activity by administration of acetylcholine precursors, cholinesterase inhibitors, or systemic cholinergic agonists had been attended by some of the difficulties with drug delivery to the brain which have previously been discussed. Intracranial cholinergic drug infusion in patients with Alzheimer's disease was start-

ed as a means of testing the validity of the cholinergic hypothesis and as an attempt at therapy for a devastating neurologic disease with no known treatment.

By delivering a muscarinic agonist into the ventricular system or cisterna magna, the problems of systemic drug inactivation, serum protein binding, and drug absorption are avoided. The use of an implantable continuous infusion pump permits long-term intracranial infusion of drug or placebo on an outpatient basis and avoids any problems of patient compliance. Pump flow rates range from 1 to 2 ml/day, an insignificant amount compared to normal daily CSF production. Because of small daily drug doses (0.05 to 0.7 mg), systemic side effects are not encountered.

Bethanechol chloride, a pure muscarinic agonist, was chosen for infusion. The drug is a polar, water-soluble molecule which is not degraded by cholinesterases and is stable in solution.

For patients with Alzheimer's disease, drug distribution to the hippocampi, locus ceruleus, reticular nucleus of the thalamus, and cerebral cortex was desired and, for the reasons described above, a drug which does not cross the blood-brain barrier when infused into the ventricular system was chosen.

Potential Complications of Central Drug Infusion

The potential advantages of central drug infusion have been discussed. There are, however, some potential disadvantages which require equal consideration. These include the operative risks of catheter placement and pump implantation, and the risk of increased neurotoxicity.

As for any neurosurgical procedure, the risks of catheter placement and pump implantation include anesthetic complications, hemorrhage, and infection. Although all these risks are low, there is probably an irreducible minimum, and some complications must be anticipated. Our personal experience here with pump implantation now includes about 40 patients who have had pumps implanted for various indications. We have encountered no significant anesthetic complications but have had one infectious and one hemorrhagic complication.

The risk of neurotoxicity with intracranial drug infusions must also be considered. Certainly, toxicity studies in animals are mandatory before considering intracranial or intraspinal infusion of drugs in patients. Although such toxicity studies decrease the risk of human neurotoxicity, some unexpected reactions to drug infusions in patients are likely to occur. We have now been infusing bethanechol chloride intracranially in patients with Alzheimer's disease for up to 20 months. One patient developed a reversible parkinsonian syndrome of rigidity and bradykinesia and another developed a reversible CSF inflammatory response which may or may not have been related to drug infusion (Harbaugh et al., 1984). Certainly, experience with more patients infused for longer periods of time will be necessary before any accurate figures on the risk of neurotoxicity are available. However, to date, drug infusions appear to be well tolerated.

The feasibility of intracranial and intraspinal administration of neurotransmitter analogues has been demonstrated (Coombs et al., 1983; Harbaugh et al., 1982, 1984). However, the value of these therapeutic endeavors over presently available therapy remains to be proven. We are conducting studies of the effect of intracranial bethanechol infusion on activities of daily living and neuropsychologic test scores in a double-blind, placebo-controlled crossover design. Preliminary studies showed family reports of decreased confusion, increased initiative, and improvements in activities of daily living during drug infusion but no subjective improvement in short-term memory was reported. A battery of short-term memory tests has also not shown a statistically significant difference between drug and placebo scores.

Almost certainly, the technique of central drug infusion for neurologic disease is more important than the outcome of any single therapeutic trial. Neurologic disorders in which abnormalities of neurotransmitter activity or availability are pathogenetically implicated and structural damage to the CNS is minimal, may prove to be the most fruitful areas for the application of this technique. Movement disorders, epilepsy, and functional

and psychiatric disease are obvious possibilities. Only time and further investigation will tell if this new approach for drug delivery to the brain will come to naught or herald a new era in neuropharmacology and functional neurosurgery.

Acknowledgments: David W. Roberts, M.D., Charles M. Culver, M.D., Ph.D., Mark C. Johnson, Ph.D., and Teddi M. Reeder, B.S., R.N., have been instrumental in developing and carrying out the Alzheimer's disease studies.

References

Aird, R.B. A study of intrathecal, cerebrospinal fluid-to-brain exchange. *Exp. Neurol.*, 86:342–358, 1984.

Blasberg, R.G., Patlak, C.S., and Fenstermacher, J.D. Intrathecal chemotherapy: Brain tissue profiles after ventriculocisternal perfusion. *J. Pharm. Exp. Ther.*, 194:73–83, 1975.

Blasberg, R.G., Patlak, C.S., and Shapiro, W.R. Distribution of methotrexate in cerebrospinal fluid and brain after intraventricular administration. *Cancer Treat. Report*, 61:633–641, 1977.

Bleyer, W.A., Poplack, D.R., Simon, R.M., et al. Concentration X time methotrexate via a subcutaneous reservoir: A less toxic regimen for intraventricular chemotherapy of central nervous system neoplasms. *Blood*, 51:835–842, 1978.

Brightman, M.W., and Reese, T.S. Junctions between intimately apposed cell membranes in the vertebrate brain. *J. Cell Biol.*, 40:648–677, 1969.

Coombs, D.W., Saunders, R.L., Gaylor, H.S., et al. Relief of continuous chronic pain by intraspinal narcotics infusion via an implanted reservoir. *JAMA*, 250:2336–2339, 1983.

Coyle, J.T., Price, D.L., and DeLong, M.R. Alzheimer's disease: A disorder of cortical cholinergic innervation. *Science*, 219:1184–1190, 1983.

Harbaugh, R.E., Coombs, D.W., Saunders, R.L., et al. Implanted continuous epidural morphine infusion system. Preliminary report. *J. Neurosurg.*, 56:803–806, 1982.

Harbaugh, R.E., Roberts, D.W., Coombs, D.W., et al. Preliminary report: Intracranial cholinergic drug infusion in patients with Alzheimer's disease. *Neurosurgery*, 15:514–518, 1984.

Katzman, R., and Hussey, F. A simple constant-infusion manometric test for measurement of CSF absorption. I. Rationale and method. *Neurology*, 20:534–544, 1970.

Lee, J.C., and Olszewski, J. Penetration of radioactive bovine albumin from cerebrospinal fluid into brain tissue. *Neurology*, 10:814–822, 1960.

Rall, D.P. Transport through the ependymal linings. *Prog. Brain Res.*, 29:159–167, 1968.

Yen, J., Reis, F.L., Kimelberg, H.K., et al. Direct administration of methotrexate into the CNS of primates. Part 2. Distribution of H3 methotrexate after intrathecal lumbar injection. *J. Neurosurg.*, 48:895–902, 1978.